UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/803,578	03/09/2001	Patrick Hwu	2026-4341	6841

23460 7590 08/26/2003

LEYDIG VOIT & MAYER, LTD
TWO PRUDENTIAL PLAZA, SUITE 4900
180 NORTH STETSON AVENUE
CHICAGO, IL 60601-6780

EXAMINER
WILSON, MICHAEL C

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 08/26/2003

16

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/803,578	HWU ET AL.	
	Examiner	Art Unit	
	Michael C. Wilson	1632	

-- The MAILING DATE of this communication appears on th cover sh et with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 June 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-8,10-12,15,40,41 and 43* is/are pending in the application.

4a) Of the above claim(s) *5* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3, 4, 6-8, 10-12, 15, 40, 41 and 43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 2, 9, 13, 14, 16-39 and 42 have been canceled. Claims 1, 3-8, 10-12, 15, 40, 41 and 43 remain pending.

Election/Restriction

1. This application contains claim 5 drawn to an invention nonelected with traverse in Paper No. 9. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Priority

2. This application repeats a substantial portion of prior Application No. 08/854723, and adds and claims additional disclosure not presented in the prior application. Since this application names an inventor or inventors named in the prior application, it may constitute a continuation-in-part of the prior application. Should applicant desire to obtain the benefit of the filing date of the prior application, attention is directed to 35 U.S.C. 120 and 37 CFR 1.78.

Or perhaps this application is a division of Application No. 08/547263, filed 10-24-95. A later application for a distinct or independent invention, carved out of a pending application and disclosing and claiming only subject matter disclosed in an earlier or parent application is known as a divisional application or "division." The divisional application should set forth only that portion of the earlier disclosure which is germane to the invention as claimed in the divisional application.

Claims 1, 3, 4, 6-8, 10-12, 15, 40, 41 and 43 are under consideration in the instant office action as they relate to lymphocytes having a chimeric receptor that is Mov-γ or a T-cell receptor (TCR) reactive with an ovarian tumor antigen and a TCR reactive with a "strong antigen" that is an "allogeneic agent" (claim 1), a lymphocyte having a TCR reactive with an allogeneic agent and a Mov-γ reactive with an ovarian tumor antigen (claim 11), a lymphocyte having a T-cell receptor reactive with a "strong" antigen that is an "allogeneic agent" and an Mov-γ reactive with an ovarian tumor antigen (claim 12), a pharmaceutical composition comprising lymphocytes having an Mov-γ reactive with an ovarian tumor antigen and "preselected" for reactivity with a "strong" antigen that is an "allogeneic agent" (claim 40), and a method of making lymphocytes comprising selecting lymphocytes that react with a "strong" antigen that is an "allogeneic agent" *ex vivo*, transducing the lymphocytes with an Mov-γ that is reactive with an ovarian tumor antigen.

Applicant's arguments filed 6-6-03, paper number 15, have been fully considered but they are not persuasive. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Specification

3. The status of application 08/547263, cited on pg 17, line 5, would need updated if it is allowed or abandoned, prior to allowance of the instant application.

Claim Rejections - 35 USC § 112

4. Claims 1, 3, 4, 6-8, 10-12, 15, 40, 41 and 43 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for reasons of record.

Claims 1 and 40 remain indefinite because it is unclear how the term "preselected" further limits the lymphocytes being claimed. The distinction between a "preselected" lymphocyte population transfected with Mov-γ and any other lymphocyte population transfected with Mov-γ cannot be determined. It is unclear to what the "selection" is prior ("pre"). Applicants argue "pre-selected" cells are described on pg 17 making the term clear. Paragraph 0053 describes methods of expanding, activating and transducing T-cells. It cannot be determined whether the cells must be expanded, activated, transduced or a combination thereof to be considered "pre-selected." It cannot be found where Examples 7 and 8 refer to "pre-selected" cells or define "pre-selected" cells as those selected for reactivity against human PBMC from another donor. If the lymphocytes react against lymphocytes from another donor, such a function should be clearly set forth.

The metes and bounds of an "endogenous T-cell receptor reactive with a preselected strong antigen" remain unclear (claim 1). It is unclear how the "strong antigen" recognized by the endogenous receptor correlates to the "tumor antigen" recognized by the chimeric receptor. The metes and bounds of a "strong antigen" cannot be determined. How strong is a "strong antigen?" Does the immune response to the antigen have to a particular type of response or can it

be any immune response? Applicants argue "strong antigens" are described as antigens capable of inducing proliferation of lymphocytes on pg 11, lines 3-7, and pg 18, lines 15-16. Therefore, applicants argue the term is definite. Applicants argument is not persuasive. The specification states "'strong antigen' as it is referred to herein relates to an antigen capable of inducing an immune proliferation of pre-selected adoptively transferred T cells. Examples of such antigens include but are not limited to alloantigens, viral agents and other foreign agents" (pg 11, lines 6-8). The examples are generic, i.e. not specific to antigens capable of inducing an immune response. The specification does not teach any antigens that induce proliferation because combinations of elements are used to activate/proliferate T cells. While applicants may be their own lexicographer, the ability of an antigen to stimulate proliferation does not have a nexus with the plain meaning of "strong." Overall, the metes and bounds of antigens capable of inducing proliferation cannot be determined.

The metes and bounds of a "strong antigen" that is an "allogeneic agent" remains unclear (now in claim 1). The metes and bounds of "allogeneic agent" cannot be determined as the phrase is not defined in the specification and does not have an art accepted meaning. It is unclear to what the agent or "strong antigen" are allogeneic as allogeneic is a relative term used to describe the histocompatibility between two things. Applicants argue "allogenic agents" are defined on pg 11, lines 7-8, as antigens derived from genetically non-identical members of the same species. While applicants may be their own lexicographer, the definition does not make sense because the plain meaning of "agents" is broad and would not be limited to antigens as

defined in the specification. Therefore, applicants definition "allogeneic agent" is repugnant to the plain meaning of "agent." It is not clear that the antigens must be isolated from genetically non-identical members of the same species or to what species the antigens are non-identical. Is the antigen allogeneic to the lymphocytes or the receptor in claim 1? Is the antigen allogeneic to the lymphocytes or the host in which the lymphocyte is activated in claim 11? Is the antigen allogeneic to the lymphocytes, the receptor or to the host in which the pharmaceutical composition is used in claim 40? "Allogeneic agents" within the group of "strong antigens" cannot be determined. While examples 7 and 8 demonstrate stimulating lymphocytes with PBMC from a different donor, the claims are not limited to stimulating lymphocytes with cells or with an agent from a donor other than the one used to isolate the lymphocytes.

Claim 4 remains indefinite because it does not clearly set forth the tumor antigen is an ovarian tumor antigen. The metes and bounds of tumor antigens "derived" from ovarian tumors is indefinite. Applicants argue the discussion of "tumor antigens" on pg 13, lines 19-26, clarifies the meaning of "derived." Applicants' argument is not persuasive. Pg 13, lines 19-26, does not define "derived" or use the term "derived." Nor does pg 13, lines 19-26, describe any ovarian tumor antigens. In addition, the definition of "tumor antigens" is unclear because it compares protein expression on tumor cells with any "normal" cell and not an equivalent non-tumor cell. Therefore, the metes and bounds of antigens "derived" from ovarian tumors cannot be determined.

Claim 8 remains indefinite because "allogeneic" is a relative term, and it remains unclear to what the peripheral blood cells are "allogeneic." It is unclear if the peripheral blood cells are "allogeneic" to the lymphocyte or the chimeric receptor. Applicants have not addressed this rejection.

Claim 8 remains indefinite because it is unclear how a "strong antigen" can comprise peripheral blood cells. Antigens are protein and do not comprise cells as claimed. The metes and bounds of which cells that are "strong antigens" as claimed is unclear. Applicants have not addressed this rejection.

The metes and bounds of the term "Mov-γ" in claim 10 remains unclear. It is unclear if the term is generic to any chimeric receptor having a variable region of a monoclonal antibody and a T-cell receptor γ chain (pg 8, line 4) or if it is limited to a chimeric receptor having a variable region of a monoclonal antibody and a T-cell receptor γ chain that is specific to ovarian tumor antigen (pg 27, line 2). Applicants argue the term was known in the art at the time of filing (Hwu et al., 1993, J. Exp. Med., Vol. 178, pg 361-366 and Hwu et al., Cancer Res., Vol. 55, pg 3369-3373). Applicants argument is not persuasive. Hwu et al. 1993 teaches Mov-γ was a chimeric receptor was made using an scFv from Mov18, a mAb that is relatively specific for human ovarian carcinoma on pg 362, col. 2, 3rd paragraph, but does not teach the structure of the scFv from Mov18 or the elements combined with the scFv to make the Mov-γ receptor. Neither the specification nor the art at the time of filing limits Mov-γ to being a chimeric receptor having an scFv from Mov18. It is unclear if Mov-γ is limited to a chimeric receptor having an scFv

from Mov18, antibody fragment that recognizes folate-binding protein or a mAb that is relatively specific for human ovarian carcinoma.

The metes and bounds of the cells encompassed by claim 11 remains unclear. It unclear to what the agent is "allogeneic." The term is allogeneic is a relative term; however, it is unclear if the agent is allogeneic to the lymphocyte or T-cell receptor. It is also unclear how the "allogeneic agent" relates to the "tumor antigen." Do the T-cell receptor and chimeric receptors recognize the same antigen? Applicants have not addressed this rejection.

The metes and bounds of antigens that are "strong antigens" in claim 12 cannot be determined as the phrase is not defined in the specification and does not have an art accepted meaning. Nor are the metes and bounds of what applicants consider "strong" antigens defined in the specification. It is unclear if the immune response to the antigen is limited to a particular immune response or if it can be any immune response. Applicants have not addressed this rejection.

It remains unclear how the "tumor antigen" and "strong antigen" in claim 12 relate. It is unclear if they are different antigens or the same antigen. Do both receptors recognize the same antigen? Applicants have not addressed this rejection.

The phrase "is activated *in vivo* with the strong antigen" (claim 12 as newly amended) is unclear because it does not clearly set forth a function or structure of the lymphocytes or how the lymphocyte was made. It is unclear if a lymphocyte that "is activated *in vivo*" is in a host or is activated in a host then removed. Therefore, it is unclear if the lymphocyte claimed is *in vivo* or

in vitro. It is unclear if the "strong antigen" is administered or if it is already present *in vivo*. Applicants argument regarding the amendment to claim 12 is not persuasive.

Claim 15 is indefinite because it is dependent upon claim 13 which has been canceled.

The metes and bounds of the cells encompassed by claim 15 remain unclear. It unclear to what the agent is "allogeneic." The term is allogeneic is a relative term; however, it is unclear if the agent is allogeneic to the lymphocyte, chimeric receptor or T-cell receptor. It is also unclear how the "allogeneic agent" relates to the "tumor antigen." Do the T-cell receptor and chimeric receptors recognize the same antigen? It is unclear how peripheral blood cells can be antigens (as in parent claim 12). Applicants have not addressed this portion of the rejection.

The metes and bounds of "strong antigen" remain unclear (claims 40 and 41). It is unclear how the "strong antigen" correlates to the "tumor antigen" recognized by the chimeric receptor. The metes and bounds of a "strong antigen" cannot be determined. How strong is a "strong antigen?" Does the immune response to the antigen have to a particular type of response or can it be any immune response? Applicants have not addressed this rejection.

The metes and bounds of cells "preselected" for reactivity remains unclear because it does not clearly set forth the function of the cells claimed (claim 41). It is unclear if applicants intend to make the claim a product by process claim or if the phrase is a functional limitation of the cell indicating it reacts with an antigen.

Claim 41 remains indefinite because it is unclear how "preselected" relates to the step of "selecting". It is unclear if "selecting" is the method of "preselecting" or if other steps are required. Applicants have not addressed this rejection.

The phrase "dual specificity lymphocytes" is indefinite (claim 41). It unclear to what two things the lymphocytes are specific. Applicants argue the phrase is defined on pg 11, lines 19-21. Applicants argument is not persuasive because the definition states such lymphocytes react with both tumor antigens and a pre-selected strong antigen and because "tumor antigens" and "pre-selected strong antigen" are not mutually exclusive. According to applicants arguments and the vague definitions of "tumor antigens" and "strong antigens" provided in the specification, a tumor antigen may be a "pre-selected strong antigen." The definition of "dual specificity lymphocytes" does not make sense because it is unclear if the phrase is limited to lymphocytes that react with two different antigens or encompasses a lymphocyte that reacts with one antigen that is both a "tumor antigen" and a "pre-selected strong antigen."

It remains unclear if folate binding protein (FBP) is an ovarian tumor antigen as elected (claim 43). It is unclear how FBP relates to the antigen recognized by the Mov-γ receptor, Mov18, or how it relates to the "strong antigen" throughout the claims. Applicants argue FBP is taught in the specification as being highly expressed in ovarian adenocarcinomas. Applicants argument is not persuasive. The claims are generic to ovarian tumor antigens, not to ovarian adenocarcinoma antigens. In addition, high expression in a tumor cell alone does not make an

antigen a "tumor antigen" according to applicants definition. It must be expressed only on tumor cells or expressed higher in tumor cells than in "normal cells" (pg 13, paragraph 0046).

Claim Rejections - 35 USC § 102

5. Claims 1, 3, 4, 6-8, 10-12, 15, 40, 41 and 43 remain rejected under 35 U.S.C. 102(e) as being anticipated by Nishimura (US Patent 5,830,755) for reasons of record.

Nishimura taught isolating tumor infiltrating lymphocytes (TIL) from colon adenocarcinoma, transfecting the cells with a chimeric receptor, Mov-γ, recognizing ovarian tumors (Mov18) (col. 37, line 54). The TIL are "preselected" as claimed because they were stimulated *in vivo* with colon adenocarcinoma and stimulated *in vitro* with antigen (col. 36, line 38-57, especially line 44). Stimulation with colon adenocarcinoma *in vivo* and an antigen *in vitro* are both "strong antigens" because the cell proliferated over a period of time which is the definition of "strong antigen" provided in the specification. The TIL have an "endogenous T-cell receptor reactive with a strong antigen" because they were isolated from MC38 colon adenocarcinoma, because they express Mov-γ, and because they recognized MC38 tumor cells in a CTL assay (col. 37, line 54, through col. 38, line 12). The MC38 tumor is "an allogeneic agent" because MC38 tumor cells were introduced into a mouse of a different species from that used to isolate the MC38 tumor cells. The MC38 tumor and the antigen *in vitro* are both "an allogeneic agent" because they are allogenic to any individual of a different strain or species than the one from which it was isolated. Claims 8 and 15 are included because cells are not antigens.

Applicants argue Nishimura did not teach the antigen was a "strong antigen" because "strong antigens" induce proliferation (pg 11, lines 2-3) and because Nishimura did not teach the antigen caused proliferation. Applicants argument is not persuasive. Claim 11 does not require a strong antigen. Furthermore, Nishimura cultured the TIL over a period of time after antigen stimulation - a clear indication that proliferation occurred - which is the definition of "strong antigen" provided in the specification.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-0120.

Questions of formal matters can be directed to the patent analyst, Dianiece Jacobs, who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-3388.

Questions of a general nature relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-1235.

If attempts to reach the examiner, patent analyst or Group receptionist are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051.

The official fax number for this Group is (703) 308-4242.

Michael C. Wilson

MICHAEL WILSON
PRIMARY EXAMINER